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10/535,042	01/09/2006	Michael R. Downes	SALK3140-01	2218

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EXAMINER	
KIM, ALEXANDER D	
ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,042	DOWNES ET AL.	
	Examiner	Art Unit	
	ALEXANDER D. KIM	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-8,10-15,18-22 and 31-33* is/are pending in the application.

4a) Of the above claim(s) *1-3,6-8,10-13,21,22 and 31-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *14,15 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on 8/5/2008), Applicants filed a response and amendment received on 11/21/2008. Said amendment cancelled Claims 4-5, 9, 16-17, 23-30 and 34-37; and amended Claims 14, 19 and 31.

Claims 1-3, 6-8, 10-15, 18-22 and 31-33 are pending in the instant Office action. Claims 1-3, 6-8, 10-13, 21-22 and 31-33 are withdrawn as non-elected inventions.

Thus, Claims 14-15 and 18-20 will be examined herein.

Withdrawn-Claim Objections

2. The previous objection of Claims 14 and 19 for reciting “molecular complex” twice is withdrawn by addition of "," in the claims.

Claim Objections

3. Claims 14-15 and 18 are objected to because of the following informalities: Claim 14 (Claims 15 and 18 dependent therefrom) recites "said structure coordinates" which should be ---said plurality of structure coordinates---- as correctly recited in Claim 19 to make claim clearer.

Appropriate correction is required.

Compliance with Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to fully comply with the requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

The structural coordinates in Appendix 1 teach two amino acid sequences since a particular atom is assigned to a linear amino acid sequence in order according to SEQ ID NO: 1. As such, the amino acid sequence disclosed within the atomic coordinates must comply with the sequence rules. Labeling using residues 248 to 270 and 286 to 475 of SEQ ID NO: 1 must be inserted into a description of the appendix in the specification or into the appendix header directly.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Maintained Objections/Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 14, 15 and 18-20 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous Claims 14, 15 and 18-20. In response to this rejection, applicants have amended cancelled Claims 4-5, 9, 16-17, 23-30 and 34-37; amended Claims 14, 19 and 31; and traverse the rejection as it applies to the newly amended claims.

Applicants argue that the instant claims are directed to methods of screening molecules to determine those which are capable of binding to a farnesoid X receptor (FXR) molecule because the claimed method require modeling a test molecule with a defined ligand binding domain of farnesoid x receptor, then determining if the test compound is capable of binding to farnesoid X receptor based on the lack of repulsive electrostatic interaction with FXR molecule in their bound state (see bottom of page 9, Remarks filed on 11/21/2008). Applicants argue that the present invention provides an

exemplary ligand binding domain (LBD; i.e., residues 248-476 of SEQ ID NO: 1) and one skilled in the art can model any compound against the exemplary LBD. Applicants argue Claim 19 and 20 further define instant invention requiring a method of screening compound to determine those with agonist, partial agonist or antagonist activity with respect to FXR molecule by any one skilled in the art by modeling a test compound with exemplary ligand binding domain (LBD; i.e., residues 248-476 of SEQ ID NO: 1). Thus, Applicants argue that they were in possession of the claimed invention at the time of instant application was filed.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The Examiner acknowledges modeling any compound using coordinates of a compound is described; and acknowledges the added recitation of amino acid residues 248-476 of SEQ ID NO: 1 in claims. However, the instant rejection is directed to a genus of methods of modeling of FXR ligand binding domain. The recitation of "comprising amino acid residues 248-476 of SEQ ID NO: 1" only further defines the structure of ligand binding domain of FXR protein and still encompasses modeling of structure coordinates of any farnesoid X receptor ligand binding domain because the breadth of claims 14, 18 and 19 encompasses the step of modeling a test compound with any structure coordinate of said farnesoid X receptor ligand binding domain fragments, or any homologue of said any FXR ligand binding domain, or a portion of coordinates in Appendix 1 (Claim 15 and 20); wherein said any FXR ligand binding domain is defined by any FXR ligand binding domain molecule or molecular complex, or any homologue of said any FXR, (see bottom of page 6 in the

previous office action mailed out on 8/5/2008). While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus," it is also acknowledged that "for inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

As previously noted, the specification discloses only a single species of the claimed genus method of modeling a test compound that potentially interact with said FXR ligand binding domain by the structure coordinates of Appendix 1 (see instant specification, page 64). However, the breadth of claims 14, 18 and 19 encompasses step of modeling a test compound with structure coordinates of any farnesoid X receptor ligand binding domain (or any homologue of said any FXR ligand binding domain) or a fragment thereof/or a portion of coordinates in Appendix 1; wherein said any FXR ligand binding domain is defined by any two or more coordinates of any FXR with any ligand binding domain (or any homologue of said any FXR); as long as the FXR protein has amino acid residues 248-476 of SEQ ID NO: 1. Claims 14 and 19 are not limited to modeling by a computer algorithm and encompass any way of modeling (drawing structure of a test compound, for example). The recited term (i.e., "plurality of structure coordinates" "set forth in Appendix 1") in Claims 15 and 20 also encompasses any portion (as small as an atom, for example) of coordinates in Appendix 1; thus, method

of claims 15 and 20 encompasses step of modeling any two sets of Cartesian coordinates from Appendix 1. Claims 14 and 19 (Claims 15, 18 and 20 dependent therefrom) recite "said structure coordinates are derived from X-ray diffraction" (emphasis added); do not limit a structure coordinate to the structure coordinates which must come from the X-ray diffraction of a FXR (or homologue thereof) crystal. Furthermore, Claim 19 recites the term “modulate the activity of said FXR molecule” and one skilled in the art would not know what kind of activity is encompassed by the instant claim; and thus the methods do not possess the full scope of claimed invention to identify any compound as an agonist, partial agonist, or antagonist of FXR molecule. The instant specification discloses a method comprising modeling by one species of Appendix 1, whereas the instant claims encompass the claimed genus method which encompasses widely variant species as described in the breadth of claims above, including a method of modeling a test compound with a "plurality of structure coordinates" (as recited in Claims 14 and 19; e.g., as small as two sets of Cartesian coordinates) of any FXR domain, any FXR homolog ligand binding domain (or any fragment thereof) for modeling a test compound. Furthermore, the prior art does is of little assistance as it does not describe any representative species for any structure coordinates for any FXR ligand binding domain (or any FXR homologue thereof), or any fragment thereof that is commensurate with the claimed scope.

Because the instant method step encompass a widely varying genus of using any FXR ligand binding domain coordinates or any FXR homolog or fragment of the coordinates thereof; the instant specification and prior art do not describe the sufficient

correlation between the structure of any FXR ligand binding domain coordinates (or homolog FXR thereof) to a function of modeling a test compound interacts with a ligand binding domain of FXR protein wherein the ligand binding domain is 248-476 of SEQ ID NO: 1. As described above, the method of genus encompassing unlimited structural variation by the claim(s) is not described sufficiently to correlate to the function of the instant invention by the specification and prior arts. Thus, given the lack of structure and functional correlation of claimed genus method, and lack of description of a representative number of structural coordinates (i.e., structural coordinate of any FXR ligand binding domain, or FXR ligand binding domain homolog thereof, for modeling a test compound); the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

6. Claims 14, 15 and 18-20 are rejected under 35 U.S.C. 112, first paragraph, first paragraph, scope of enablement, because the specification, while being enabling for a method of screening a molecule capable of binding to a human FXR ligand binding domain (i.e., residues 248-476 of SEQ ID NO: 1); or identifying a compound with agonist, partial agonist, or antagonist activity to a human FXR ligand binding domain (i.e., residues 248-476 of SEQ ID NO: 1) by a method comprising: modeling a test compound with the structure coordinates of Appendix 1 *in silico*; **does not** reasonably provide enablement for a method encompassing any step of modeling a test compound with any structure coordinate of farnesoid X receptor ligand binding domain (or any

homologue of said any FXR ligand binding domain), or a fragment thereof, or any portion of coordinates in Appendix 1; wherein said any FXR ligand binding domain is defined by any two or more coordinates of any FXR with any ligand binding domain (or any homologue of said any FXR); or any fragment thereof; wherein the FXR protein has ligand binding domain of comprising amino acid residues 248-476 of SEQ ID NO: 1.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous Claims 14, 15 and 18-20. In response to this rejection, applicants have amended cancelled Claims 4-5, 9, 16-17, 23-30 and 34-37; amended Claims 14, 19 and 31; and traverse the rejection as it applies to the newly amended claims.

Applicants argue that the specification enables any person skilled in the art to make and/or use the invention commensurate in scope with the claims; and alleges that the Examiner acknowledged as such by recitation in the previous Office action page 8, item 7). Applicants argue the present claims are supported by providing substantial information for screening compounds capable of binding to any FXR because the FXR members share structurally conserved domains including the ligand binding domain (LBD); thus, utilizing the instant exemplary LB, one skilled in the art can model any molecules for determining the ability of the test compound to bind to a FXR molecule or the agonist partial agonist or antagonist activity of the test compounds with respect to a

FXR molecule or fragment thereof (emphasis added, see bottom of page 12, Remarks filed on 11/21/2008).

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. Regarding Applicant's understanding of what is recognized as being enabled by the Examiner's statement in the beginning of the instant rejection, contrary to Applicant's remark, the Examiner only acknowledged certain species among the claimed entire scope as being enabled which includes *in silico* modeling methods using the coordinate of Appendix 1, which is used to support Applicants' argument (i.e., "the specification enables any person skilled in the art to make and/or use the invention commensurate in scope with the claims" (see page 12, lines 7-8, beginning of second paragraph, Remarks filed on 11/21/2008). The Examiner's disagree with the position made by the Applicants that is "the specification enables any person skilled in the art to make and/or use the invention commensurate in scope with the claims", which indeed is not supported by or in view of the acknowledgement by the Examiner. The Examiner clearly stated previously that "At the time of the invention, methods of modeling a test compound with a potential interaction between the compound and a protein using a 3-D structure of a protein to a known structural coordinate and computing a computer model of a ligand to ligand binding pocket using a known binding pocket structure. However, while methods of predicting or identifying a test compound association with a protein using a known three dimensional structure of protein and binding pocket of a protein using a set of structure coordinates was known, Lambert et al. (US Patent Application Publication

2004/0137518) acknowledges that "potential or existent homology models cannot provide the necessary degree of specificity" in the *in silico* design of modulators (p. 3, §0017)" (see middle of page 11 in the previous office action mailed on 8/5/2008). Thus, a species from the scope of claimed invention is enabled *in silico* method steps: that is the step of using the coordinates of Appendix 1. The way the claims are written, the recitation of "comprising amino acid residues 248-476 of SEQ ID NO: 1" can be interpreted as only describing the FXR protein itself; but not necessarily limiting the method step of using a model, specially the claimed modeling step that includes the ligand binding domain of any two or more (a plurality) structural coordinates of the ligand binding domain of FXR molecule or fragment thereof; wherein the structural coordinates may encompasses any homologue of said FXR molecule or molecular complex thereof. Thus, simply placing a chemical structure(s) next to the structure model of any ligand binding site (e.g., homolog or fragment thereof) of FXR protein does not make one skilled in the art to make and use the full scope of claimed invention as described by the breadth of claims below. According to MPEP 2111.04 [R-3], regarding recited clause "whereby", "The determination of whether each of these clauses is a limitation in a claim depends on the specific facts of the case. In Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005), the court held that when a "whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention." Id. However, the court noted (quoting Minton v. Nat 'l Ass 'n of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)) that a "whereby clause in a method claim is

not given weight when it simply expresses the intended result of a process step positively recited.'" (emphasis added). Thus, recitation of "whereby those compound..." in Claim 14(Claims 15 and 18 therefrom) and "whereby those compounds ..." in Claim 19 (Claim 20 dependent therefrom) in the claimed method are merely intended results of recited process steps and are not an active step and thus have patentable weight. One skilled in the art would require undue experimentation without sufficient direction and guidance for the claimed method that is screening compounds to determine those with agonist, partial agonist, or antagonist activity to a FXR molecule by screening binding molecule(s).

As similarly noted in the previous office action mailed on 8/5/2008, the breadth of the claims encompass a method step of modeling a test compound with structure coordinates of any farnesoid X receptor ligand binding domain (or any homologue of said any FXR ligand binding domain) or a fragment thereof, or a portion of coordinates in Appendix 1; wherein said any FXR ligand binding domain is defined by any two or more sets of Cartesian coordinates of any FXR with any ligand binding domain (or any homologue of said any FXR); or any fragment thereof; where in the FXR protein has the residues 248-476 of SEQ ID NO: 1 which is only describing the structure of FXR protein molecule and not the structure that is used in the *in silico* step in view of any plurality, any fragment, and or any homologue structure coordinate of said FXR protein. Claims 14 and 19 are not limited to modeling by a computer algorithm and encompass any way of modeling (drawing structure of a test compound, for example). The recited term (i.e., "plurality of structure coordinates" "set forth in Appendix 1") in Claims 15 and 20 also

encompasses any portion (as small as an atom, for example) of coordinates in Appendix 1; thus, method of claims 15 and 20 encompasses step of modeling any two coordinates from Appendix 1. Claims 14 and 19 (Claims 15, 18 and 20 dependent therefrom) recite "said structure coordinates are based on X-ray diffraction data"; however, the homologue thereof does not limit a structure coordinate to the structure coordinates which must comes from the X-ray diffraction of said FXR crystal. Furthermore, Claim 19 recites the term “modulate the activity of said FXR molecule” and one skilled in the art would not know what kind of activity is encompassed by the instant claim; and thus, the claims do not possess the full scope of claimed invention to identify any compound with agonist, partial agonist, or antagonist of FXR molecule.

The scope of the claims is not commensurate with the enablement provided by the specification, particularly with respect to the recited method step of modeling a test compound with any FXR ligand binding domain, which is defined by any plurality of structure coordinates (including as small as two coordinates) from the Appendix 1, for example. In this case, the specification is enabling only for a method for modeling a test compound by the coordinates of Appendix 1 *in silico*.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: At the time of the invention, methods of modeling a test compound with a potential interaction between the compound and a protein using a 3-D structure of a protein to a known structural coordinate and computing a computer model of a ligand to ligand binding pocket using a known binding pocket structure. However, while methods of predicting or identifying a test compound association with a protein

using a known three dimensional structure of protein and binding pocket of a protein using a set of structure coordinates was known, Lambert et al. (US Patent Application Publication 2004/0137518) acknowledges that "potential or existent homology models cannot provide the necessary degree of specificity" in the *in silico* design of modulators (p. 3, §0017). Flower D.R. (2002, Drug Design Cutting Edge Approaches, The Royal Society of Chemistry, p. 21-27) also acknowledge that "a well-established technique and automated methods. Problem still exist, however, the fitting together of protein domains in a multi-domain protein, the determination of the most likely conformation of protein loops, the correct positioning of amino acid side chains, flexible ligand docking – to name only a few" (emphasis added, see p 25, lines 18-21). Further, it was well-known in the prior art that polypeptides having disparate functions can share similar 3-D structures. For example, Hegyi et al. [*J Mol Biol* (1999) 288:147-164] teaches that an isomerase, an oxidoreductase, a hydrolase, and a lyase all share the same TIM-barrel fold (p. 148, left column, and Figure 1). Thus, the full scope of encompassed method of using any structure coordinates of any homologue of FXR molecules (including any variant (or derived) structure coordinates of Appendix 1) cannot predict and/or identify a compound that binds, or with agonist or antagonist activity because of the high unpredictability of test compounds based on model structures, wherein the model structure encompasses very widely varying structure coordinates. Thus, a skilled artisan would have recognized that there was a high level of unpredictability in the method of modeling a test compound with any FXR ligand binding domain structure coordinates; or any model structure coordinates of any FXR homologue from any

portion of known 3-D structure coordinates Appendix 1, for the relevant use of the instant method for predicting and/or identifying a agonist or antagonist compound, wherein the step involves just modeling of a test compound (in silico or not) with any ligand binding domain of any FXR, or any homolog thereof, or any portion thereof; or any plurality of coordinates in Appendix 1, or a portion thereof; wherein the FXR protein has amino acid residues 248-476 of SEQ ID NO: 1.

The amount of direction provided by the inventor and The existence of working examples: The specification suggest a method for evaluating a potential association of an entity with a protein or active site using a model with a certain RMSD compared 3-D structure of the human IRRK having structural coordinates of Figure 3. The prior art by Hubbard et al. (1997, The EMBO Journal, Vol. 16, p. 5573-5581) teach a method of using the 3-D structure of human IRRK, which is within the scope of the instant claims. The specification fails to disclose a method for evaluating a potential of an entity to associate with a protein using a 3-D structure of any other protein or variant structures thereof that is encompassed by the claims. Further, the specification fails to provide guidance for method for displaying 3-D structures of any other protein that is encompassed by the scope of the claims.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of modeling a test compound with a FXR protein by creating a three dimensional structure in a computer using the coordinates of Appendix 1 was established, it was not routine in the art to create a unlimited number of 3-D structures (including a coordinates of any FXR homologues, or fragment thereof) as

encompassed by the claims without guidance as to which of those structure coordinates are useful in accordance with the asserted utility of the claimed invention, *i.e.,* to provide useful structural information that assists the predictability and/or identification of a test compound with agonist or antagonist activity to the ligand binding domain of FXR receptor comprising amino acid residues 248-476 of SEQ ID NO: 1 *in vivo*.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, the genus method for predicting a molecule capable of binding to FXR molecule, or for identifying a compound with agonist, partial agonist, or antagonist activity to FXR molecule, according to the full scope of claimed method which comprises modeling a test compound, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Withdrawn-Claim Rejections - 35 USC § 101

7. The previous rejection of Claims 14, 15 and 18-20 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter, is withdrawn by virtue of Applicants' argument and reconsideration by the Examiner.

Withdrawn-Claim Rejections - 35 USC § 102

8. The previous rejection of Claims 14, 15 and 18-20 are rejected under 35 U.S.C. 102(b) as being anticipated by McKinney (Environmental Health Perspectives, 1989, Volume 82, pages 323-336) is withdrawn by virtue of Applicants' amendment (i.e., addling limitation of "comprising amino acid residues 248-476 of SEQ ID NO: 1" for the ligand binding domain of FXR molecule).

Conclusion

9. Claims 14-15 and 18-20 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered section in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 11AM-7:30PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/
Examiner, Art Unit 1656

/SUZANNE M. NOAKES/
Primary Examiner, Art Unit 1656